U.S. DEPARTMENT OF COMMERCE, PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER
33891R005

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)
10/009559

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/SE00/01267	15 June 2000	15 June 1999

TITLE OF INVENTION
RECEPTOR AGONISTS AND ANTAGONISTS

APPLICANT(S) FOR DO/EO/US --- Staffan Skogvall

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ■ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.

2. □ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.

3. ■ This express request to begin national examination procedures (35 U.S C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(l).

4. ■ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. ■ A copy of the International Application as filed (35 U S.C. 371(c)(2))
a.□ is transmitted herewith (required only if not transmitted by the International Bureau)b ■ has been transmitted by the International Bureau (see Form 308) c. □ is not required, as the application was filed in the United States Receiving Office (RO/US).

6. □ A translation of the International Application into English (35 U S C. 371(c)(2))

7. ■ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
a.■ are transmitted herewith (required only if not transmitted by the International Bureau)
b. □ have been transmitted by the International Bureau.
c. □ have not been made; however, the time limit for making such amendments has NOT expired.
d. □ have not been made and will not be made.

8. □ A translation of the amendments to the claims under PCT Article 19 (35 U S.C. 371(c)(3)).

9. □ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4))

10. □ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ■ An Information Disclosure Statement under 37 CFR 1.97 and 1.98. (w/ copy of PTO-1449 and each reference cited therein and Int'l Search Rept)

12. □ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3 28 and 3.31 is included.

13. □ A FIRST preliminary amendment.
□ A SECOND or SUBSEQUENT preliminary amendment.

14. □ A substitute specification.

15. □ A change of power of attorney and/or address letter.

16. ■ Other items or information:

a) International Search Report (PCT/ISA/210) (original "A2" version and revised "A3" version),
b) International Preliminary Examination Report (PCT/IPEA/409) **including the amended claim set to be prosecuted;**
c) PCT Publ. WO 00/76500
d) Formal Drawing Set (included with international application)
e) Form PCT/IB/308
f) Form PCT/IPEA/402
g) PCT Request (Form PCT/RO/101)

10/009559

ATTORNEY'S DOCKET NUMBER 2380.R005

JC13 Rec'd PCT/PTO 14 DEC 2001

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)

17. ■ The following fees are submitted:	CALCULATION	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO $890.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) $670.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2) $760.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $970.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) $96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$970.00	
Surcharge of $130.00 for furnishing the oath or declaration later than □ 20 □ 30 months from the earliest claimed priority date (37 CFR 1.495(c)).	$ -	

Claims	Number Filed	Number Extra	Rate		
Total Claims	20 - 20 =	0	x $18.00	$ .00	
Independent Claims	3 - 3 =	0	x $84.00	$ .00	
Multiple dependent claim(s) (if applicable)			+ $280.00	280.00	
			TOTAL OF ABOVE CALCULATIONS =	$1250.00	
Reduction by ½ for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28)				$ 625.00	
			SUBTOTAL =	$ 625.00	
Processing fee of $130.00 for furnishing the English translation later than □ 20 □ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$ -	
			TOTAL NATIONAL FEE =	$625.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property. +				$ .00	
			TOTAL FEES ENCLOSED =	$625.00	
				Amount to be refunded	$
				charged	$

a. ■ A check in the amount of $ 625.00 to cover the above fees is enclosed.
b. □ Please charge my Deposit Account No. 02-4300 in the amount of $ ____ to cover the above fees. A duplicate copy of this sheet is enclosed.
c. ■ The Commissioner is hereby authorized to charge any additional fees which may be required with respect to any deficiency in the above noted "Basic National Fee", or credit any overpayment to Deposit Account No. 02-4300 .

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

SMITH, GAMBRELL & RUSSELL, LLP
1850 M Street, NW - Suite 800
Washington, DC 20036

Tel: (202) 659-2811
Fax: (202) 659-1462

SIGNATURE

Dennis C. Rodgers - 32,936
NAME REGISTRATION NO

Date: December 14, 2001

1/prts

RECEPTOR AGONISTS AND ANTAGONISTS

Field of the Invention

The present invention relates to a compound having agonist activity to the 5-HT_4 receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compound is administered. The present invention also relates to a compound having antagonist activity to the 5-HT_3 receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compound is administered.

Background of the Invention

Receptors of the 5-HT (serotonin; 3-(β-aminoethyl)-5-hydroxyindole) type are well known and occur throughout the body, e.g. in the airways, and their relevance has mainly been reported in conjunction with treatment of CNS, muscle and gastric disorders, as disclosed in *e.g.* WO 98/18458 and US 5 246 935. In such treatments, compounds having agonist activity to a 5-HT_1 type receptor are often used. As examples of other 5-HT receptors, mention can be made of receptors of the 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 type. For a recent review of 5-HT receptors, see Gerhardt, C.C., van Heerikhuizen, H., *Eur. J. Pharm.*, 334, 1-23 (1997), which is incorporated herein by reference.

A review of typical agonists and antagonists of various 5-HT receptors is disclosed in R.A. Glennon, Neuroscience and Biobehavioral Reviews, 14, 35-47 (1990), the whole content of which is incorporated herein by reference.

SU 1 701 320 A1 discloses the use of serotonin for treatment of acute asthma attacks. This reference does not suggest any receptor mechanism for serotonin, which is a compound with both a contracting and a relaxing effect on the airways, as is further discussed herein below.

In the RBI Handbook or Receptor Classification and Signal Transduction, 3rd Edition, 1998, RBI, One Strathmore Road, Natick, MA 01760-2447, USA, Editor: Keith J. Watling are compounds having agonist or antagonist activity to various receptors disclosed.

Disclosure of the Invention

The present invention is based on the novel finding that certain 5-HT receptors are of utmost importance in regulating bronchocontraction. In summary, it is disclosed herein that compounds having agonist activity to the 5-HT_4 receptor bring about a bronchorelaxing action upon administration thereof, and are therefore suitable as agents for treatment of bronchocontraction disorders. It is also disclosed herein that compounds having antagonist activity to the 5-HT_3 receptor, are suitable agents in the treatment of bronchocontraction disorders. Methods for treatment of bronchocontraction disorders are also disclosed.

As used herein, the expression bronchocontraction disorder refers to an abnormal increase of the force development of the smooth muscle, resulting in a reduced diameter in some or all of the airways of the lungs and/or the extrapulmonary airways. Said expression also refers to reduction of airflow caused by swelling, oedema, plasma extravasation or mucous secretion caused by *e.g.* asthma or any other disorder related thereto.

Accordingly, the present invention relates, in one of its aspects, to a compound having agonist activity to the 5-HT_4 receptor for use as a medicament. In another aspect it relates to use of said compound in the manufacture of a medicament for therapeutic or prophylactic

treatment of a human or animal body, wherein the medicament is intended for treatment of disorders involving bronchocontraction, such as asthma.

In a preferred embodiment, the invention relates to the use of a compound having agonist activity to the 5-HT_4 receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, wherein said agonist has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%.

The present invention also relates, in another aspect, to a compound having antagonist activity to the 5-HT_3 receptor for use as a medicament. In another aspect it relates to use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of a human or animal body, wherein the medicament is intended for treatment of disorders involving bronchocontraction, such as asthma.

In a preferred embodiment, the invention relates to the use of a compound having antagonist activity to a 5-HT_{2a} receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, wherein said antagonist has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%.

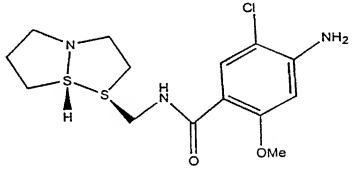
Said bronchocontraction may also occur in conjunction with such disorders as *e.g.* emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions, including schizophrenia.

The present invention also relates to the use of a compound having antagonist activity to a 5-HT_3 receptor in combination with a compound having agonist activity to the 5-HT_4 receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders in-

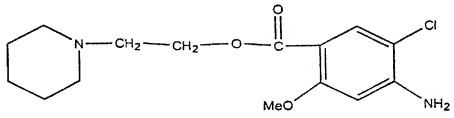
volving bronchocontraction. In a preferred embodiment said compound having agonist activity is serotonin or a derivative thereof having agonist activity to the 5-HT_4 receptor. This combination of the 5-HT_3 receptor antagonist and the agonist increases the beneficial effect of serotonin, particularly in the presence of a serotonin uptake inhibitor (SRI). Further, the compounds having agonist activity to the 5-HT_4 receptor to be used according to the present invention are also useful in the present combination embodiment. In particular, said medicament is intended for treatment of asthma and disorders related thereto.

According to the present invention several known substances are able to stimulate the 5-HT_4 receptor, without activating the contracting 5-HT_3 receptor, thereby, surprisingly, generating a relaxing effect on the bronchocontraction. Such agonist compounds are selected from the group comprising the substances SC 53116, ML 10302, RS 67506 and BIMU 8, which are defined below, as well as the more unspecific 5-carboxamidotryptamine, and derivatives and pharmaceutically acceptable salts thereof having the same or essentially the same relaxation effect.

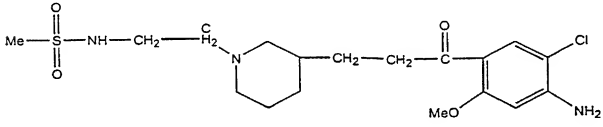
The invention also relates to the use of one or more of the above-mentioned agonist compounds: SC 53116, i.e. 4-amino-5-chloro-N-[[1S, 7aS)-hexahydro-1H-pyrrolizin-1-yl]methyl]-2-methoxy-benzamide, having the structural formula:



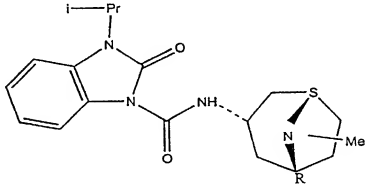
ML 10302, i.e. 4-amino-5-chloro-2-methoxy-benzoic acid-2-(1-piperidinyl)ethylester, having the structural formula:



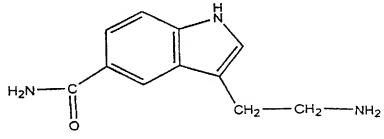
RS 67506, i.e. N-[2-[4-[3-(4-amino-5-chloro-2-methoxyphenyl)-3-oxopropyl]-1-piperidinyl]ethyl]-methanesulfonamide monohydrochloride, having the structural formula:



BIMU 8, i.e. 2,3-dihydro-N-[(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(1-methylethyl)-2-oxo-1H-benzimidazole-1-carboxamide monohydrochloride, having the structural formula:



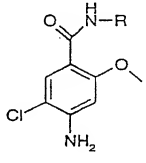
5-carboxamidotryptamine (5-CT), having the structural formula:



ADR932, BIMU 1, BRL 20627, BRL 24682, BRL 24924, Cinitaprid, Cisapride, DAU 6215, DAU 6236, 5-HT, 5-hydroxy-N,N-dimetyltryptamin, 3-Me-8-OH-DPAT, ML-1035, 5-metoxytryptamin, Metoclopramide, Mosapride, 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), Prucalopride, R 076186, R 093877 (prucalopride), Renzapride, RS 17017, RS 23597-190, RS 56532, RS 57639, RS 67333, RS 67532, RU 28253 SB 204070, SB 205149, SC-52491, SC-49518, SK-951, SDZ 216-454, SR59768, TKS159, VB20B7, Y-34959, YM-47813, YM-53389, YM-09151, Zacopride, Zelmac (SDZ HTF919; tegaserod) and derivatives and pharmaceutically acceptable

salts thereof having essentially the same relaxing effect, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, wherein said agonist has the capacity of reducing the bronchocontraction by at least 30%, preferably at least 60%, most preferably at least 90%.

Most of the different 5-HT_4 agonists can be divided in certain groups, wherein each group contains a common structural element. The largest group, and also the basis for several others, are the benzamides. They all contain the structural element 4-amino-5-chloro-2-methoxy benzamide and are further developments of the first 5-HT_4 agonist, metoclopramide.



These compounds are also potent 5-HT3-antagonists:

- 3-(4-Allylpiperazin-1-yl)-2-quinoxalinecarbonitrile
- 5-[(Dimethylamino)methyl]-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole
- 3-(1-Piperazinyl)-2-quinoxalinecarbonitrile
- Granisetron
- RS-25259-197
- SEC-579, Mirisetron
- SC-52491
- KB-6933
- BRL 46470, Ricasetron
- Lerisetron
- KAE-393/YM-114
- AS-5370
- DAT-582
- N-3256
- SDZ 214-322
- KF-20170
- Lurosetron
- Galdansetron
- ONO-3051
- CP-93318
- Batanopride
- GR 67330
- SDZ 206-830
- QICS 205-930
- BRL 24682
- LY 258-458
- Zacopride, S(-)Zacopride, R(+)Zacopride
- RP 62203
- SDZ 206-792
- BRL 47204
- SDZ 210-204
- LY-211-000
- MCPP
- MK 212
- Mianserin
- SDZ 210-205

- Bufotenine
- Pitozifen
- Indalpine
- Cizapride
- Cyproheptadine
- 2-Methyl-5HT
- Amitriptyline
- LY 278-989
- Imipramine
- Phenylbiguanide
- TFMPP
- 5,7-DHT
- RU 24969
- Ritanserin
- NAN-190
- Mepyramine
- Metergoline
- Methysergide

These compounds are also potent 5-HT4-agonists:

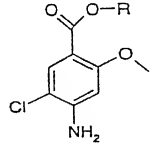
- Bufotenine
- 5-MeO-N,N,DMT
- GR 113,808
- α-Metyl-5HT

Another common feature is a basic nitrogen in a side chain from the amide nitrogen. This basic nitrogen is often a part of a sterically locked system. Examples of substances from this group are:

BRL 20627, BRL 24682, BRL 24924, Cisapride, Metoclopramide, ML-1035, Mosapride, R076186, Renzapride, RS 67506, Cinitapride, SB 205149, SC-49518, SC-52491, SC-53116, TKS 159, Y-34959, YM-09151, YM-47813, Zacopride.

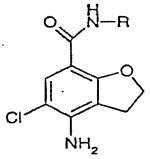
Thus, a structure-activity relation study performed indicates that a benzene ring and a basic nitrogen in the same plane as the ring and at a distance of 8±1 Å from the center of the benzene ring is required. The nitrogen should be locked in that position with a view to obtaining selectivity against other 5-HT receptors. A lipophilic group on the basic nitrogen also seems to be important for the agonistic action. Further, a heteroatom having a free electron pair close to the indole nitrogen in tryptamine seems to give a positive effect.

Benzoic acid esthers are modifications of the benzamide theme:

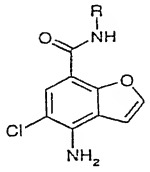


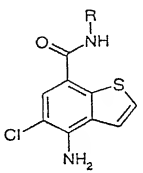
The only difference is that the amide group has been replaced with an esther group. Examples are ML 10302, RS 57639, and SR 59768.

Another variant of the basic theme is to introduce the methoxy group into a ring, thereby arriving at a 2,3-dihydro-bensofuran-7-karboxamide group. Examples are ADR 932, Prucalopride (=R 093877); and SK-951.

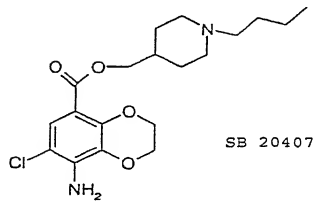


Benzofuranes and benzotiophenes are also contemplated,



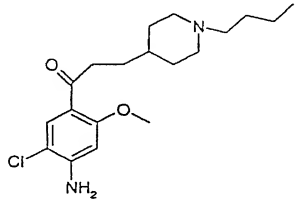


as well as the benzodioxan



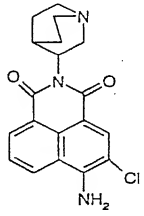
SB 204070

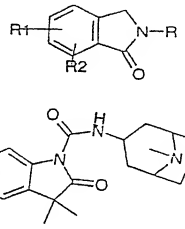
Still another variant is based on the discovery that the benzoic acid antagonist RS 23597 (an esther) was transformed to an agonist if it was converted to a ketone



, e.g. RS 67333 and RS 17017.

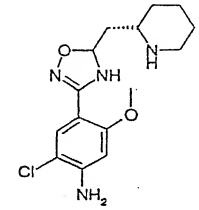
The basic concept also applies for naphtalimides, e.g. RS 56532.





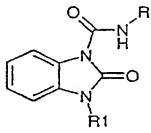
Benzindolones are also contemplated

The amide fuction may also be replaced with an oxadiazol ring.



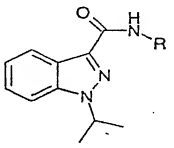
, e.g. YM-53389

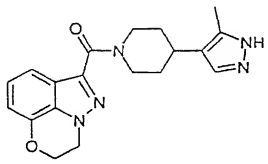
Benzimidazolone-1-carboxamides



, e.g. BIMU 1, BIMU 8, DAU 6215, and DAU 6236, are also contemplated.

The carboamides

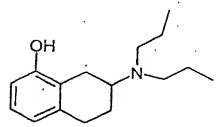




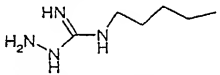
are also contemplated.

Some indols are olso useful as 5-HT_4 agonists, e.g. 5-methoxytryptamine, 2-methylserotonine, and 5-hydroxy-N,N-di-methyltryptamine.

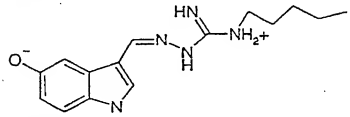
Other tested substances useful as 5-HT_4 agonists according to the present invention are



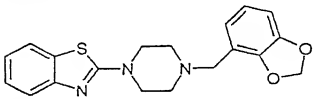
SDZ 216-454



Zelmac=SDZ HTF 919



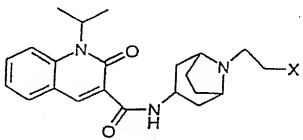
VB20B7



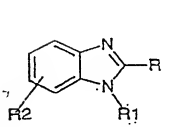
It should be noted that many of these substances may be quaternized on the nitrogen in the side chain without losing the activity.

The most active agonist at present seems to be Zelmac.

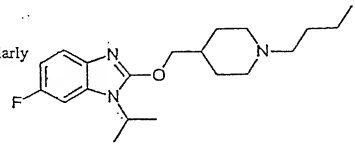
Benzokinolinones



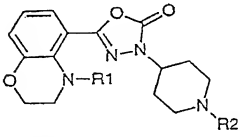
Further 5-HT4 agonist structures useful according to the present invention



, particularly

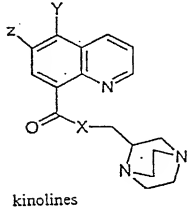


2-piperidinmethylethers of bensimidazol

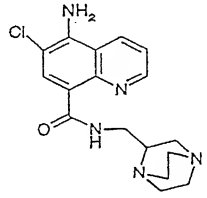


oxadiazalon based substance

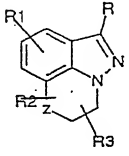
Arylcarbamate derivatives of 1-piperidineethanol
4-amino-5-chloro-2methoxybenzoic acid esters,
e.g. ML10302, RS 57639 and SR59768
4-amino-5-chloro-2-methoxy-N-((2S,4S)-1-ethyl-2-hydroxymethyl-4-pyrrolidinyl)benzamide,e.g. TKS159
thiophene carboxamide derivatives 3 (a-j)
5. Azabicyclo(x.y.z) derivatives
2-piperazinylbenzoxazole derivatives
2-piperazinylbenzothiazole derivatives, e.g. VB20B7
clebopride
Sandoz compound 1b



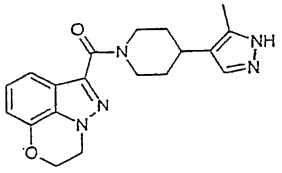
, particularly

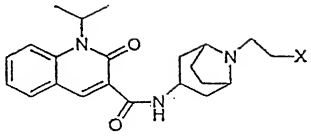


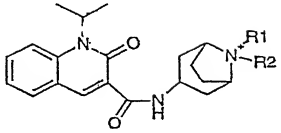
kinolines



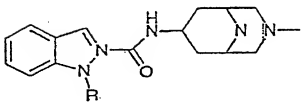
, particularly

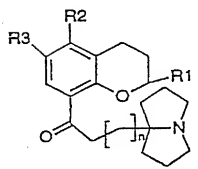




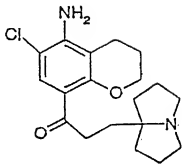


Q

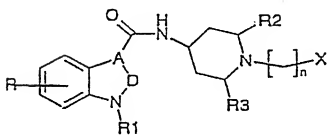


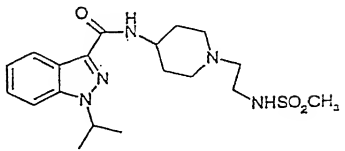


, particularly



bensopyranes





The most preferred 5-HT_4 receptor agonist is RS 67333.

According to the present invention several known antagonist compounds are, surprisingly, able to influence the 5-HT_3 receptor, thereby generating a contraction reducing effect, i.e. a relaxation effect, and are selected from a group comprising 4-Ph-N-Me-quipazine, ADR-851, ADR-882, Alosetron, Anpirtoline, Azasetron (=Y 25130), BIMU 1, BMY 33462, BRL 24924, BRL 43694, BRL 46470 A, CF 109203 (=BIM), Chlorpromazine, Cilansetron (=KC 9946), Cisapride, Clozapine, Cyameazine, DAT-582 (=(R)AS-5370), Diltiazem, Dolasetron (=MDL 74156), Dolasetron mesilat (=MDL 73147 EF), Droperidol, FK 1052, Fluphenazone, Galanolactone, GK 128, GR 38032 F, GR 65630, Gramisetron (=Kytril=BRL 43694), GR-H, GYKl-48903, ICI 169369, ICS 205-930, Ifenprodil, Iodophenpropit, Itasetron (=DAU 6215), KB-6922, KB-R 6933, KF 17643, KF 18259, L-683877, Litoxetine, LY 278584, McNeil-A-343, MDL 72222, MDL 72699, Metoclopramid, Mirtazapine, Mosapride, N-3389, N-metylquipazin, Ondansetron (=GR 38032 F), Palonosetron, Pancopride, Perphenazine, Prochlorperazine (=Stemetil), Quipazine, QX 222, (R)-zacopride, Ramosetron (=YM 060), Renzapride, RG 12915, RS-25259, RS 42358-197, RS 56532, RS-056812-198, RS-25259-197, RS-56812, S-apomorfin, SC-53116, SDZ 216-525, SDZ 322, SN-307, Talipexole, Thioperamide, TMB 8, Trifluoperzine, Trimebutine, Tropisetron (=ICS 205-930=Rifenserin), VA 21 B 7, Way 100289, WAY-100579, WAY-SEC-579, Y 2513, YM 114 (=KAE-393), Zatosetron (=LY 277359) and pharmaceutically acceptable salts thereof having the same or essentially the same contraction reducing effect.

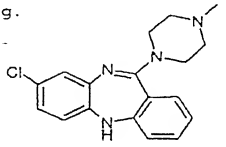
The present invention also relates to the use of one or more of the above-mentioned 5-HT_3 antagonist compounds and to derivatives and pharmaceutically acceptable salts thereof having essentially the same contraction reducing effect, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving

bronchocontraction, wherein said antagonist has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%.

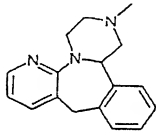
The 5-HT_3 receptor is a ligand modulated ion channel. The known anxiety repressing bensodiazepines influence not only 5-HT_3 but also several other receptors for different neurotransmittors. Several potent specific 5-HT_3 antagonists exist today, of which ondansetron, tropisetron, granisetron, and dolasetron are commercial pharmaceuticals, however, not against disorders involving bronchocontraction.

Some of the 5-HT_3 receptor antagonists are at the same time 5-HT_4 receptor agonists. However, for a substance to be active as a 5-HT_3 receptor antagonist, the distance from the aromatic center to the basic nitrogen should be about 7,5 Å and no large substituents are tolerated on the basic nitrogen. In contrast, for 5-HT_4 receptor agonists the corresponding distance is about 8 Å, and a large lipophilic group may be bound to the basic notrogen, thereby obtaining a better binding to 5-HT_4.

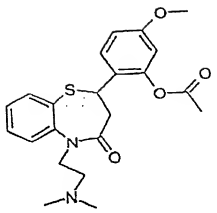
The 5-HT_3 antagonist may be divided in certain classes with the basis on the chemical structure. Some are unspecific, e.g.



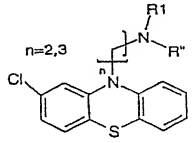
benzazepines, e.g. mirtazapine



benztiazephines, e.g. diltiazem

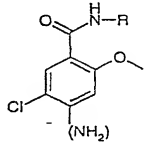


and fentiazines



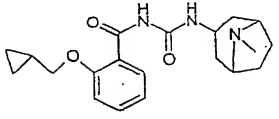
, e.g. perphenazine, chlorpromazine, stemetil

Some are 5-HT_4 agonists, e.g. benzamides



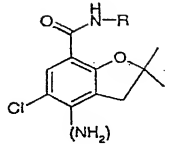
(cisapride, zacopride, mosapride, metoclopramide, pancropride, BRL 24924, BMY 33462)

and



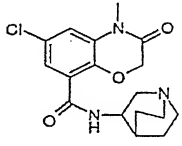
WAY 100289

2,3-dihydro-benzofuran-7-carboxamides



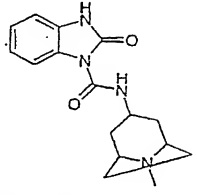
(e.g. zatosetron=LY 277359, ADR 851)

1,4-bensoxazin-8-carboxamides



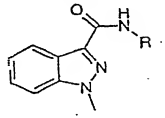
, e.g. azasetron (=Y25130)

benzimidazolones



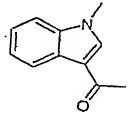
, e.g. itasetron (=DAU 6215)

indazol-3-carboxamides

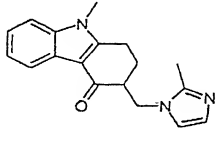


, e.g. N 3389, LY 278584, DAT 582

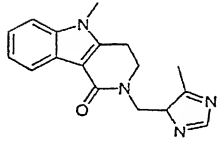
The latter group reminds most of the specific 5-HT_3 antagonists, which after contains the group



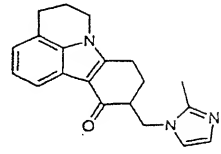
in different forms, such as



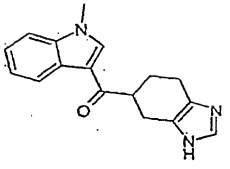
ondansetron



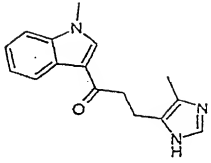
alosetron



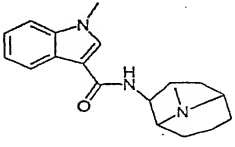
cilansetron



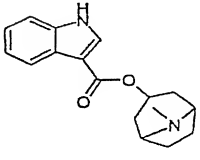
ramosetron



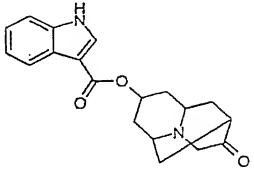
GR 65630



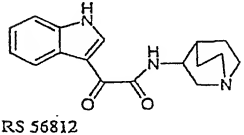
granisetron



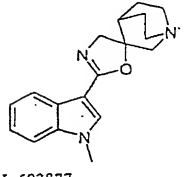
tropisetron



dolasetron

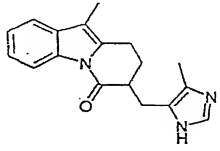


RS 56812



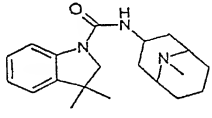
L 683877

In one group of substances the structure has been inverted and the carbonyl group has been placed on the indoline nitrogen



FK 1052

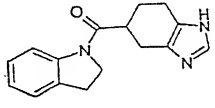
This substance is unique by being an antagonist against both 5-HT_3 and 5-HT_4.



BRL 46470 A

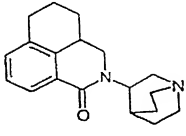
BRL 46470A binds to two different positions of the receptor.

A further development is the so-called bisindoles

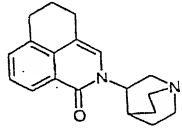


YM 114

Another group is the isoquinoline-1-ones

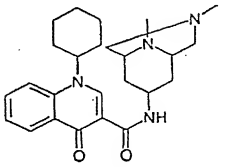


palonosetron (=RS 25259-197)

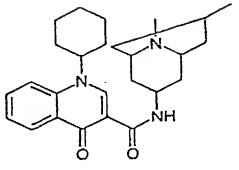


RS 42358-197

and the quinoline-3-carboxamides

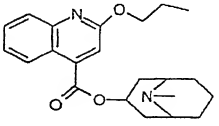


WAY-SEC 579

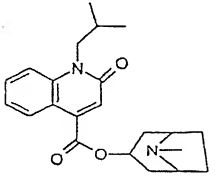


Mirisetron (=WAY 100579)

Also the quinoline-4-carboxylates are active antagonists

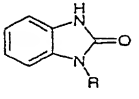


, e.g. KF 17643



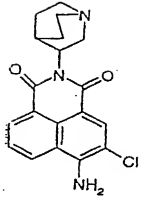
, e.g. KF 18259

Other compounds are benzimidazolones



e.g. droperidol (neurolidol, etc.), itasetron (DAU6215),

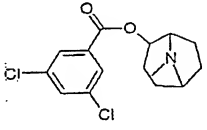
and the naphtimides



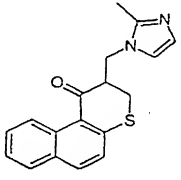
RS 56532

, e.g. RS 56532

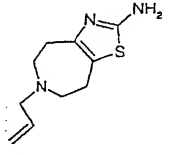
A unique single structure is MDL 72222, which also is a specific 5-HT_3 antagonist



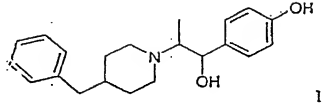
Other specific structures are



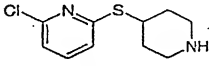
GK 128



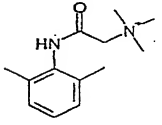
Talipexole



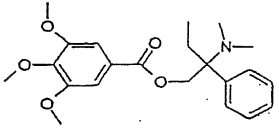
Ifenprodil



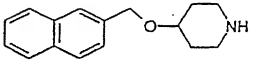
Anpirtoline



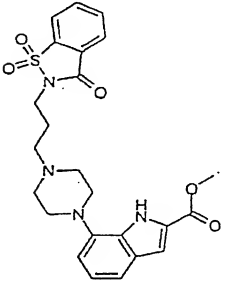
QX 222



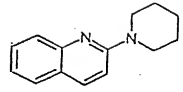
Trimebutine



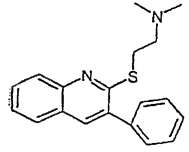
Litoxetine



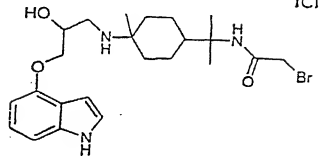
SDZ 216-525



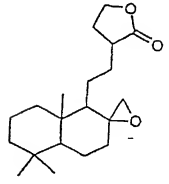
Quipazine



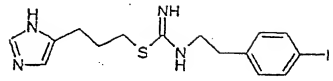
ICI 169369



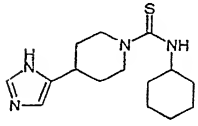
BIM



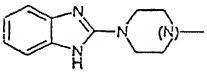
Galanolakton



iodophenpropit



thioperamide, and



2-piperidin- and 2-piperazin-benzimidazoles.

The most preferred 5-HT_3 receptor antagonist is tropanyl-3,5-dimethylbenzoate.

The present invention also relates to a method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of the compound according to the present invention having agonist activity to the 5-HT_4 receptor. Preferably, said method relates to the treatment of asthma and disorders related thereto.

The present invention also relates to a method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a compound according to the present invention having antagonist activity to a 5-HT_3 receptor. Preferably, said

method relates to treatment of asthma and disorders related thereto.

Further, the present invention relates to a method for treatment of disorders involving bronchocontraction, wherein the above-mentioned combination of agonist(s) and antagonist(s) is administered.

The expression "has the capacity of reducing the pathological bronchocontraction by at least ….%" used throughout the present patent application means that the compound in question reduces the contraction in the airways caused (1) either by the underlying disease (asthma etc) or (2) by the administration of 5-HT or other substances with 5-HT_3-activating properties. The level of contraction in the airways can, for instance, be determined by spirometric measurements of the Forced Expiratory Volume (FEV1), compared to the normal value for healthy people. Alternatively, the expiratory capacity for a patient can be compared to his own FEV1 during periods of relatively little obstructive problems.

As appears from Fig. 1, the contractile component often manifests itself as a reduction or a complete elimination of the 5-HT induced relaxation, rather than in an increase of force from the control (pre-exposure) level. In the case of "specific" agonists to the 5-HT_4 receptor, this sustained relaxing effect is achieved because the contractile 5-HT_3 receptor is not affected; only the relaxing 5-HT_4 receptor is activated. In the case of antagonists to the 5-HT_3 receptor, this effect is achieved due to direct blocking of the 5-HT_3 receptor, whereby the unspecific agonists to the 5-HT_4 receptor, such as 5-HT, can act without also causing contraction by the 5-HT_3 receptor.

It should be noted that the medicament prepared according to present invention in each embodiment may optionally include two or more of the above outlined compounds.

Further, in the embodiment when the compound having 5-HT_3 antagonist activity is administered, optionally together with complementary serotonin or derivatives thereof, a serotonin uptake inhibitor can be added with a view to amplifying the relaxing effect.

The typical daily dose of the medicament prepared according to the invention varies within a wide range and will depend on various factors such as the individual requirement of each patient and the route of administration.

Said medicament may be prepared as a composition adapted either for administration via the respiratory tract or for oral, intravenous, topical, intraperitoneal or subcutaneous administration, in association with one or more pharmaceutically acceptable carriers, diluents or adjuvants that are well known in the art.

Moreover, said medicament is preferably administered via the respiratory tract in the form of *e.g.* an aerosol or an air-suspended fine powder. However, in some cases a useful alternative to administration via the respiratory tract may be oral, topical, parenteral, subcutaneous, transdermal or rectal administration, wherein *e.g.* tablets, capsules, powders, microparticles, granules, syrups, suspensions, solutions, transdermal patches or suppositories are utilized.

Brief Description of the Drawing

Fig. 1 depicts the effects of 5-HT and the selective 5-HT_4 agonist RS 67333 on the spontaneous tone in human in vitro preparations. Note that 5-HT only gives a transient relaxation, while selective 5-HT_4 agonists give a strong sustained relaxing effect.

Detailed Description

The subject-matter of the present invention was inter alia deduced from animal experiments, where a specific behavior of the airway smooth muscle called "spontaneous tone" was examined. The spontaneous tone, which involves a spontaneous continuous contraction in

the airway smooth muscle, was studied due to a suspicion that defective regulation of the spontaneous tone could be an important cause of the bronchoconstriction observed in asthmatic patients.

The examinations of the spontaneous tone were performed in accordance with the methods disclosed in the thesis "*Regulation of spontaneous tone in guinea pig trachea*" by S.Skogvall, Department of Physiological Sciences, Lund University, 1999, which is incorporated herein by reference. As evidenced by these examinations, the airways normally display a highly regular type of oscillating tone if exposed to physiological conditions, and the oscillating tone can be reversibly affected by administration of various substances. When the epithelium is removed, the preparations instead display a strong, smooth type of tone.

In short, the animal experiments in said thesis showed that the spontaneous tone to a large degree is controlled by powerful regulating factors released from neuroepithelial endocrine (NEE) cells.

Later experiments, not included in the thesis, have revealed that one of the regulating factors is serotonin, also called 5-HT, which exerts agonist action on the receptors 5-HT_1, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 as well as on 5-HT_2 receptors.

Additional experiments have shown that when 1 µM serotonin was added to denuded airway smooth muscle preparations from the guinea-pig displaying a strong, smooth spontaneous tone, the average force level was increased significantly, *i.e.* a contraction was observed. A contractile effect of serotonin on airway smooth muscle has been reported in *e.g.* Skogvall, S., Korsgren, M., Grampp, W., *J. Appl. Phys.*, 86:789-798, 1999. However, when 10 µM of serotonin was added, the spontaneous tone was significantly suppressed to a level of about half the force observed in control (drug-free) conditions. The spontaneous tone returned to approximately its normal level when the

preparations were again exposed to control conditions. Thus, it has now surprisingly been shown that serotonin brings about contraction of the airways at low concentrations and relaxation at high concentrations, consequently having a dual effect on the airways.

Furthermore, it has been shown that when the contracting 5-HT_{2a} receptor was blocked with ketanserin, the 5-HT, i.e. serotonin, induced almost no contraction, but instead only a significant relaxation. Similar experiments have also been performed on human in vitro preparations, from patients undergoing lobecotomy or pulmectomy due to lung cancer. It was found that in this tissue, 5-HT was even more potent in relaxing the airway smooth muscle than in guinea pig. In human tissue, already 1 μM 5-HT induces a significant relaxation of the spontaneous tone.

Human airways are generally considered to display only a weak contraction when exposed to 5-HT. Nevertheless, examinations on spontaneous tone on human in vitro preparations have shown that 5-HT indeed has a contractile component also in this tissue. However, this contraction takes a longer time to develop than in guinea pig and the contractile effect is seen as a termination of the relaxation, rather than an increase of tone from the baseline. In guinea pig trachea, the contraction reaches a maximum after approximately 10 min, and this is followed by a considerable reduction of tone. However, human preparations instead induce a maximum relaxing effect after 5-10 min, which disappears gradually during the following 30-45 min (see Fig 1). The transient nature of the 5-HT relaxation is most likely caused by a simultaneous activation of the fast, relaxing 5-HT_4 receptor, and a slower activation of the contracting receptor, which in human airways surprisingly has been found to be the 5-HT_3 receptor. This is clear, because activation of the relaxing 5-HT_4 receptor by a substance that lacks 5-HT_3 receptor activating properties (such as RS 67333),

results in a relaxation that is persistent and not transient (see Fig. 1).

It has previously been suggested that 5-HT or 5-HT analogues may be useful in the treatment of bronchoobstructive diseases. In SU 1 701 320 it is suggested that the 5-HT, i.e. serotonin, may be of use as an addition to standard beta2 receptor stimulation. However, from our experiments it seems clear that 5-HT is not effective or useful as the only treatment for e.g. asthmatic disorders, because of the transient relaxing effect by 5-HT (see Fig. 1). If instead, as we propose herein, a 5-HT analogue that lacks the 5-HT_3 activating properties is given, the relaxing effect is persistent, and not transient.

In summary, it has now been discovered that agonist action on the 5-HT_4 receptor results in a relaxing effect, whereas agonist action on 5-HT_3 receptors results in a contractile effect. In conclusion, the dual effect of serotonin is most likely a result of its agonist action on the relaxing 5-HT_4 receptor as well as on the contracting 5-HT_3 receptor.

It was also deduced from these experiments that compounds having agonist activity to the 5-HT_4 receptor, while having only low or no agonist activity to a 5-HT_3 receptor, therefore are useful as agents for treatment of bronchocontraction disorders.

Thus, the present invention relates to the use of compounds having agonist activity to the 5-HT_4 receptor in the manufacture of a medicament intended for treatment of bronchocontraction disorders, whereby said compounds have the strong bronchorelaxing effect of serotonin but have substantially no contractile effect. As mentioned above, the compounds used according to the present invention have only low or no agonist activity to 5-HT_3 receptors.

In the above mentioned experiments it has also been shown that compounds having antagonist activity to a

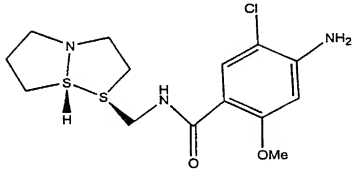
5-HT_3 receptor are useful as agents for treatment of bronchocontraction disorders, since they are capable of blocking the contractile effect of a compound having agonist activity to a 5-HT_3 receptor. The compounds according to the present invention having antagonist activity to the 5-HT_3 receptor may even be administered together with serotonin in the form of a complement to the serotonin content already present in the body with a view to obtaining an amplified contracting effect; or with any other substance having agonist activity to the 5-HT_3 receptor; or with a serotonin uptake inhibitor.

Said administration can be simultaneous or sequential, and a powerful relaxing effect on the bronchi can be achieved in this manner. Thus, the present invention also relates to the combined use of a compound having antagonist activity to a 5-HT_3-receptor and a compound having agonist activity to the 5-HT_4 receptor, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction.

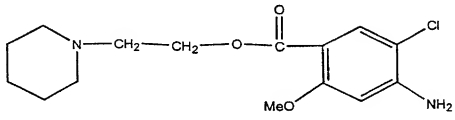
CLAIMS

1. Compound having agonist activity to a 5-HT_4 receptor, and derivatives and pharmaceutically acceptable salts thereof having agonist activity to the 5-HT_4 receptor for use as a medicament for treatment of disorders involving bronchocontraction.

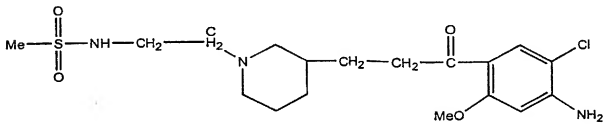
2. Compound according to claim 1, wherein said compound has the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound is chosen from the group comprising SC 53116, i.e. 4-amino-5-chloro-N-[[1S, 7aS)-hexahydro-1H-pyrrolizin-1-yl]methyl]-2-methoxy-benzamide, having the structural formula:



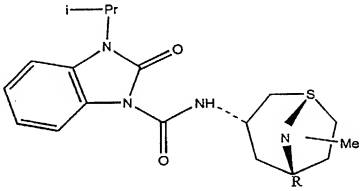
ML 10302, i.e. 4-amino-5-chloro-2-methoxy-benzoic acid-2-(1-piperidinyl)ethylester, having the structural formula:



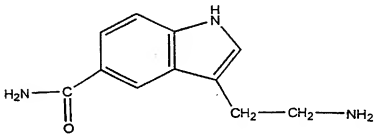
RS 67506, i.e. N-[2-[4-[3-(4-amino-5-chloro-2-methoxyphenyl)-3-oxopropyl]-1-piperidinyl]ethyl]-methanesulfonamide monohydrochloride, having the structural formula:



BIMU 8, i.e. 2,3-dihydro-N-[(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(1-methylethyl)-2-oxo-1H-benzimidazole-1-carboxamide monohydrochloride, having the structural formula:



5-carboxamidotryptamine (5-CT), having the structural formula:

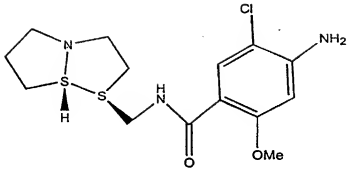


ADR932, BIMU 1, BRL 20627, BRL 24682, BRL 24924, Cinitaprid, Cisapride, DAU 6215, DAU 6236, 5-HT, 5-hydroxy-N,N-dimetyltryptamin, 3-Me-8-OH-DPAT, ML-1035, 5-metoxytryptamin, Metoclopramide, Mosapride, 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), Prucalopride, R 076186, R 093877 (prucalopride), Renzapride, RS 17017, RS 23597-190, RS 56532, RS 57639, RS 67333, RS 67532, RU 28253 SB 204070, SB 205149, SC-52491, SC-49518, SK-951, SDZ 216-454, SR59768, TKS159, VB20B7, Y-34959, YM-47813, YM-53389, YM-09151, Zacopride, Zelmac (SDZ HTF919; tegaserod).

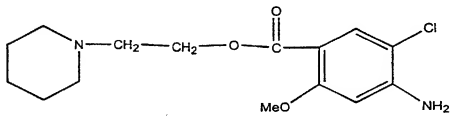
3. Compound according to claim 2, wherein said bronchocontraction appears in asthma and disorders related thereto, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions including schizophrenia.

4. Use of one or more compounds according to claims 1 and 2 having agonist activity to a 5-HT_4 receptor, and derivatives and pharmaceutically acceptable salts thereof having agonist activity to the 5-HT_4 receptor, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, optionally together with a serotonin uptake inhibitor.

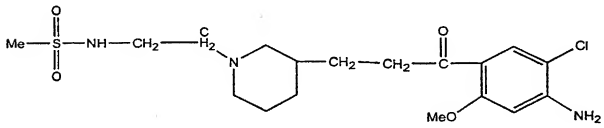
5. Use according to claim 4, wherein said one or more compounds has/have the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound(s) is/are chosen from the group comprising SC 53116, i.e. 4-amino-5-chloro-N-[[1S, 7aS)-hexahydro-1H-pyrrolizin-1-yl]methyl]-2-methoxy-benzamide, having the structural formula:



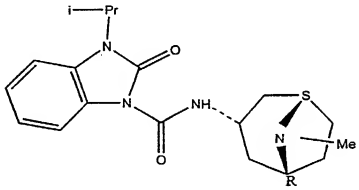
ML 10302, i.e. 4-amino-5-chloro-2-methoxy-benzoic acid-2-(1-piperidinyl)ethylester, having the structural formula:



RS 67506, i.e. N-[2-[4-[3-(4-amino-5-chloro-2-methoxyphenyl)-3-oxopropyl]-1-piperidinyl]ethyl]-methanesulfonamide monohydrochloride, having the structural formula:

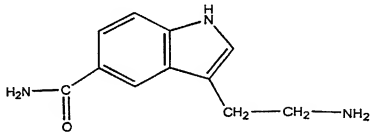


BIMU 8, i.e. 2,3-dihydro-N-[(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(1-methylethyl)-2-oxo-1H-benzimidazole-1-carboxamide monohydrochloride, having the structural formula:



5

5-carboxamidotryptamine (5-CT), having the structural formula:



10

ADR932, BIMU 1, BRL 20627, BRL 24682, BRL 24924, Cinitaprid, Cisapride, DAU 6215, DAU 6236, 5-HT, 5-hydroxy-N,N-dimetyltryptamin, 3-Me-8-OH-DPAT, ML-1035,
15 5-metoxytryptamin, Metoclopramide, Mosapride, 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), Prucalopride, R 076186, R 093877 (prucalopride), Renzapride, RS 17017, RS 23597-190, RS 56532, RS 57639, RS 67333, RS 67532, RU 28253
20 SB 204070, SB 205149, SC-52491, SC-49518, SK-951, SDZ 216-454, SR59768, TKS159, VB20B7, Y-34959, YM-47813, YM-53389, YM-09151, Zacopride, Zelmac (SDZ HTF919; tegaserod).

6. Use according to claims 4 and 5, wherein said disorder having pathological bronchocontraction is asthma and disorders related thereto, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions including schizophrenia.

7. A method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a compound according to claim 1.

8. Compound having antagonist activity to a 5-HT_3 receptor, and derivatives and pharmaceutically acceptable salts thereof having antagonist activity to the 5-HT_3 receptor for use as a medicament for treatment of disorders involving bronchocontraction.

9. Compound according to claim 8, wherein said compound has the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound is chosen from the group comprising 4-Ph-N-Me-quipazine, ADR-851, ADR-882, Alosetron, Anpirtoline, Axasetron (=Y 25130), BIMU 1, BMY 33462, BRL 24924, BRL 43694, BRL 46470 A, CF 109203 (=BIM), Chlorpromazine, Cilansetron (=KC 9946), Cisapride, Clozapine, Cyameazine, DAT-582 (=(R)AS-5370), Dilalazem, Dolasetron (=MDL 74156), Dolasetron mesilat (=MDL 73147 EF), Droperidol, FK 1052, Fluphenazone, Galanolactone, GK 128, GR 38032 F, GR 65630, Gramisetron (=Kytril=BRL 43694), GR-H, GYKl-48903, ICI 169369, ICS 205-930, Ifonprodil, Iodophenpropit, Itasetron (=DAU 6215), KB-6922, KB-R 6933, KF 17643, KF 18259, L-683877, Litoxetine, LY 278584, McNeil-A-343, MDL 72222, MDL 72699, Metoclopramid, Mirtazapine, Mosapride, N-3389, N-metylquipazin, Ondansetron (=GR 38032 F), Palonosetron, Pancopride, Perphenazine, Prochiorperazine (=Stemetil), Quipazine, QX 222, (R)-zacopride, Ramosetron (=YM 060), Renzapride, RG 12915,

RS-25259, RS 42358-197, RS 56532, RS-056812-198, RS-25259-197, RS-56812, S-apomorfin, SC-53116, SDZ 216-525, SDZ 322, SN-307, Talipexole, Thioperamide, TMB 8, Tritiuoperzine, Trimebutine, Tropisetron (=ICS 205-930=Rifenserin), VA 21 B 7, Way 100289, WAY-100579, WAY-SEC-579, Y 2513, YM 114 (=KAE-393), Zatosetron (=LY 277359), preferably tropanyl-3,5-dimethylbenzoate.

10. Compound according to claim 9, wherein said bronchocontraction appears in asthma and disorders related thereto, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions including schizophrenia.

11. Use of one or more of the compounds according to claims 8 and 9 and including ketanserin having antagonist activity to a 5-HT_3 receptor, and derivatives and pharmaceutically acceptable salts thereof having antagonist activity to the 5-HT_3 receptor, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, optionally together with a serotonin uptake inhibitor.

12. Use according to claim 11, wherein said one or more compounds has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound(s) is/are chosen from the group comprising 4-Ph-N-Me-quipazine, ADR-851, ADR-882, Alosetron, Anpirtoline, Axasetron (=Y 25130), BIMU 1, BMY 33462, BRL 24924, BRL 43694, BRL 46470 A, CF 109203 (=BIM), Chlorpromazine, Cilansetron (=KC 9946), Cisapride, Clozapine, Cyameazine, DAT-582 (=(R)AS-5370), Dilalazem, Dolasetron (=MDL 74156), Dolasetron mesilat (=MDL 73147 EF), Droperidol, FK 1052, Fluphenazone, Galanolactone, GK 128, GR 38032 F, GR 65630, Gramisetron (=Kytril=BRL 43694), GR-H, GYKl-48903, ICI 169369, ICS 205-930, Ifonprodil, Iodophenpropit, Itasetron (=DAU 6215), KB-6922, KB-R 6933, KF 17643, KF 18259, L-683877, Litoxetine,

LY 278584, McNeil-A-343, MDL 72222, MDL 72699, Metoclopramid, Mirtazapine, Mosapride, N-3389, N-metylquipazin, Ondansetron (=GR 38032 F), Palonosetron, Pancopride, Perphenazine, Prochiorperazine (=Stemetil), Quipazine, QX 222, (R)-zacopride, Ramosetron (=YM 060), Renzapride, RG 12915, RS-25259, RS 42358-197, RS 56532, RS-056812-198, RS-25259-197, RS-56812, S-apomorfin, SC-53116, SDZ 216-525, SDZ 322, SN-307, Talipexole, Thioperamide, TMB 8, Tritiuoperzine, Trimebutine, Tropisetron (=ICS 205-930=Rifenserin), VA 21 B 7, Way 100289, WAY-100579, WAY-SEC-579, Y 2513, YM 114 (=KAE-393), Zatosetron (=LY 277359), preferably tropanyl-3,5-dimethylbenzoate.

13. Use of one or more compounds according to claims 11 and 12 in combination, either simultaneously or sequentially, with a compound having agonist activity to the 5-HT_4 receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, optionally together with a serotonin uptake inhibitor.

14. Use according to claim 13, wherein said compound having agonist activity to the 5-HT_4 receptor is serotonin and derivatives thereof or a compound according to claims 1 and 2.

15. Use according to claims 11-14, wherein said disorder having pathological bronchocontraction is asthma and disorders related thereto, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions including schizophrenia.

16. A method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a compound according to claims 11-14.

17. Composition comprising a combination of the compounds defined in claims 13 and 14 for use as a medicament for treatment of disorders involving bronchocontraction.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 December 2000 (21.12.2000)

PCT

(10) International Publication Number
WO 00/76500 A2

(51) International Patent Classification[6]: A61K 31/4045, A61P 11/08, 11/06

(21) International Application Number: PCT/SE00/01267

(22) International Filing Date: 15 June 2000 (15.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

9902251-9	15 June 1999 (15.06.1999)	SE
9902252-7	15 June 1999 (15.06.1999)	SE
60/139,633	17 June 1999 (17.06.1999)	US
60/139,632	17 June 1999 (17.06.1999)	US
PCT/SE00/00819	28 April 2000 (28.04.2000)	SE

(71) Applicant *(for all designated States except US)*: RESPIRATORIUS AB [SE/SE]; Sölvegatan 41, S-223 70 Lund (SE).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: SKOGVALL, Staffan [SE/SE]; Flygelvägen 33, S-224 72 Lund (SE).

(74) Agent: AWAPATENT AB; Box 5117, S-200 71 Malmö (SE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR (utility model), KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *Without international search report and to be republished upon receipt of that report.*

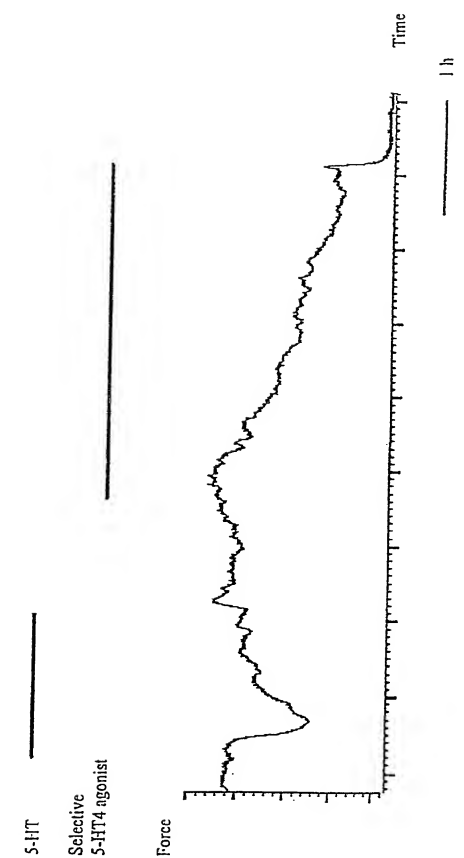
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: RECEPTOR AGONISTS AND ANTAGONISTS

(57) Abstract: The present invention relates to a compound having agonist activity to the 5-HT_4 receptor for use as a medicament and to the use of said compounds in the manufacture of a medicament for use in therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compounds are administered. The present invention also relates to a compound having antagonist activity to the 5-HT_3 receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for use in therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compounds are administered.

WO 00/76500 A2

Fig 1



10009559 - 060402

UNITED STATES (Form BDWY-I)
Patents & Design Patents
Sole & Joint Inventors
Convention & Non-convention
PCT & Non-PCT
This form cannot be amended. Altered or changed after it is signed.
(For use only for inventors who understand the English language.)

Declaration and Power of Attorney
United States Patent Application

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name.
I believe I am the original, first and sole inventor *(if only one name is listed below)* or an original, first and joint inventor *(if plural names are listed below)* of the subject matter which is claimed and for which a patent is sought on the invention entitled

RECEPTOR AGONISTS AND ANTAGONISTS

FEB 2002

10009559

(check one)
- ☐ is attached hereto.
- ☒ was filed as U.S. Application No. _____ on 7 December 2001 and *(if applicable)* was amended on _____.
- ☐ was filed as PCT International Application No. _____ on _____ and *(if applicable)* was amended under PCT Article 19 on _____.

(I authorize any attorney appointed below to insert information in the preceding blanks.)

I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign and PCT application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America listed in this Declaration. I have also identified below any foreign application for patent or inventor's certificate or PCT international application having a filing date before that of the application(s) on which priority is claimed:

Foreign/PCT Application No.	Country	Filing Date	Priority Claimed? (yes/no)
9902251-9	Sweden	15 June 1999	Yes
9902252-7	Sweden	15 June 1999	Yes
PCT/SE00/00819	Sweden	28 April 2000	Yes

I hereby claim the benefit under Title 35, United States Code, § 120 or §365(c) of any United States application and PCT international application designating the United States of America listed in this Declaration and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application or PCT international application in the manner provided by the first paragraph of Title 35, United States Code, § 112. I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. Application No.	Filing Date	*Status (patented/pending/abandoned?)*
PCT/SE00/01267	15 June 2000	

I hereby claim priority benefits under Title 35 United States Code § 119(e) of any U.S. provisional application(s) listed below:

U.S. Provisional Application No.	Filing Date
60/139,632	17 June 1999
60/139,633	17 June 1999

I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Joseph A. DeGrandi (17446), Robert G. Weilacher (20531), Richard G. Young (20628), Michael A. Makuch (32263), Dennis C. Rodgers (32936), Thomas L. Evans (35805), Frank C. Cimino, Jr. (39945), Carolyn Favorito (39183), George A. Metzenthin (P41995), and Steven W. Collier (P42429).

Send all correspondence to Beveridge, DeGrandi, Weilacher & Young, L.L.P., Suite 800, 1850 M Street, N.W., Washington, D.C. 20036. Facsimiles may be sent to (202) 659-1462. Direct all telephone calls to (202) 659-2811.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor: Staffan SKOGVALL
Residence *(city, state, country)*: Lund, Sweden
Post office address: Flygelvägen 33, 224 72 LUND, SWEDEN
Citizenship: Swedish

Signature: _____ Date: 7 January 2002

☐ Additional inventors and/or prior applications are listed in attached Supplemental Sheet(s).